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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,504	10/18/2000	Marc K. Wallack	11221/5	5100

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/691,504	Wallack et al.
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 18, 2000* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-107* is/are pending in the application.

4a) Of the above, claim(s) *1-17, 24, 25, 27, 28, 39-54, 65, 66, 68, 69, 97, 9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6, 9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's supplemental response to the restriction requirement, received on 10/1/02, has been entered. Applicant's original response received on 6/6/02 has previously been entered. Claims 1-107 are pending in the instant application. Of these, claims 1-17, 24-25, 27-28, 39-54, 65-66, 68-69, 97-98, and 100-101 have been withdrawn from prosecution as being drawn to subject matter non-elected with traverse in paper nos. 11, and 13. Claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 are currently under examination at this time. An action on the merits follows.

Election/Restriction

Applicant's election with traverse in paper no. 11 of the subject matter of group II is acknowledged. Applicant's further election with traverse in paper no. 13 of the species IL-2 as both the first and second immunostimulatory molecule is also acknowledged. Applicant's traversal is on the grounds that the claims are sufficiently related to be properly presented in a single application. Applicant's argument is not found compelling for reasons of record. In brief, Inventions I and III are related as process of making and process of using the product. Since the product is not allowable, restriction is proper between said method of making and method of using (MPEP § 806.05(I); Inventions I and III are distinct from invention II in that invention II includes a second independent vaccinia virus which encodes a different immunostimulatory molecule from that encoded by the vaccinia virus used to infect the antigen presenting cells.

Further, the methods of immunizing using the compositions of invention II are substantially different from those of invention I in that invention II requires the direct administration of a vaccinia virus to a mammal. As such the methods utilize different substantially different reagents with substantially different biological functions. This restriction/election requirement is therefore deemed proper and made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of generating an anti-tumor immune response and methods of inhibiting tumor growth in a mammal comprising the administration at or near a regional lymph node of an immunogenic composition comprising a recombinant vaccinia virus encoding IL-2 and autologous or syngeneic DCs or DC/MNs pulsed with an antigen preparation comprising enucleated cytosol and cell membranes from tumor cells infected with a recombinant vaccinia virus encoding IL-2, wherein the antigen preparation is derived from tumor cells which the same tumor cells or the same type of tumor cells present in the mammal, does not reasonably provide enablement for said methods and immunogenic

compositions wherein the immunogenic composition comprises any type of antigen presenting cells pulsed with tumor lysate from any type of tumor, or wherein the immunogenic composition is administered to any location in the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for generating anti-tumor immune responses capable of inhibiting tumor growth in a mammal by administering any antigen presenting cell pulsed with tumor lysate from any type of tumor infected with vaccinia virus encoding IL-2 (VV-IL-2). At the time of filing, the art teaches that in order to generate an effective immune response which includes both cellular and humoral immunity, an antigen of interest must be presented by professional antigen presenting cells which express both MHC class I and class II and thus are capable of stimulating both CD8+ and CD4+ T cells respectively. Activation of CD4+ T cells is particularly important as activated CD4+ T cells express co-stimulatory molecules necessary for B cell activation and maturation and secrete cytokines which co-stimulate both B cells and CD8+ T cells. Whereas MHC class I is expressed from most types of nucleated cells, MHC class II expression is limited to professional antigen presenting cells such as macrophages and dendritic cells. The dendritic cell in particular has been identified as the crucial antigen presenting cell for priming T cells. Pardoll teaches that, "Because DCs are felt to be the primary cell necessary fro activating virgin T cells, Their role in priming immunologic responses is now considered central" (Pardoll, page 528, column 1). Pardoll teaches that the

particular potency of dendritic cells in activating T cells derives from the fact that these cells express 50-fold higher levels of MHC molecules than macrophages and other antigen presenting cells, they express extremely high levels of T cell adhesion and co-stimulatory molecules, and they express T cell specific chemokines (Pardoll, page 530, column 1). Thus, it is clear that the art at the time of filing considered presentation of antigen by professional antigen presenting cells, and dendritic cells in particular, as essential for priming an antigen-specific T cell response. It is further noted that the applicant's working examples in mice and in humans are limited to the use of cultured dendritic cells or dendritic/monocytic cells. The specification fails to provide guidance for using antigen presenting cells other than dendritic/monocytic cells. Therefore, based on the state of the art of priming T cells, the unique features of the dendritic cell, the limitation of the working examples to dendritic/monocytic cells, and the breadth of the claims, it would have required undue experimentation to practice the instant invention with any antigen presenting cell.

The specification further fails to provide guidance for administering DC/MCs which are allogeneic or xenogeneic. At the time of filing, it was well known that both xenogeneic and allogeneic transplantation of tissue into mammals results in rapid immunological rejection of the transplanted tissue (Kaufman et al., (1995), Annu. Rev. Immunol., Vol. 13, see entire document). In particular, the art teaches that hyperacute rejection of xenogeneic tissues can occur in as little as 2 hours, (Kaufman et al., supra, pages 339-367). The specification does not provide sufficient guidance concerning the generation of therapeutic anti-tumor immune responses following the administration of allogeneic or xenogeneic DCs. The working examples provided utilize

autologous or syngeneic cells, thus avoiding the rejection issue. The examples provide no guidance or evidence which demonstrates that allogeneic or xenogeneic DCs pulsed with tumor lysate are capable of persisting in a transplanted immunocompetent host for a sufficient period of time to generate and sustain anti-tumor immune responses. Thus, based on the nature of allogeneic and xenogeneic transplant rejection, the lack of guidance or working examples concerning the administration of allogeneic or xenogeneic cells in the specification, and the breadth of the claims, it would have required undue experimentation to practice the full scope of the invention as claimed.

Furthermore, the specification does not provide any guidance regarding the ability of immune responses generated against any tumor antigens present in tumor lysate to protect against the growth of a tumor which does not express the antigens present in the tumor lysate. At the time of filing, it was well-known that most types of tumors express tumor antigens which are unique to either the particular tumor, or tumor type (Pardoll, page 526). While the idea of "shared" tumor antigens exists in the literature, there is little data to support the concept. The specification does not teach tumor cells which express "shared" tumor antigens or identify and particular "shared" antigens. Further, the specification's working examples pulse the DCs with tumor oncolysate from the either the same tumor present in the host, or with tumor cells which are the same class of cells as the host tumor- see for example the description of the clinical trail in patients with melanoma which received autologous DC/MCs pulsed with oncolysate from established human melanoma cell lines. The specification provides insufficient guidance and

evidence to enable the treatment of tumors in a host by administering DCs or DC/MCs pulsed with tumor lysate from a tumor which does not express any of the same tumor antigens as the host tumor.

The specification also does not provide an enabling disclosure for administering the disclosed immunogenic compositions by any route of administration to any site in the mammal to be treated. The specification's working examples inject the immunogenic compositions at or near the site of major peripheral lymph nodes. The specification does not provide sufficient guidance for priming therapeutic immune responses with the cells and virus of the instant invention using any route and site of administration. At the time of filing, it was well-known that T cell priming occurs in the lymph nodes. In order for dendritic cells to prime a naive T cell, it must first migrate to a lymph node (Nestle et al., page 328). Nestle et al. teaches that, "[i]njecting DCs in a peripheral tissue site (such as skin) or intravenously may lead to a substantial loss of DCs during migration into spleen or lymph node" (Nestle et al., page 328, column 2). Thus, based on the nature of T cell priming, the nature of dendritic cell migration, the art recognized unpredictability of priming immune responses using intradermal, subcutaneous, or intravenous administration of dendritic cells, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the full scope of the invention as claimed.

The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of

working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Ultimately, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). For the reasons discussed in detail above, the specification only provides an enabling disclosure for methods of generating an anti-tumor immune response and methods of inhibiting tumor growth in a mammal comprising the administration at or near a regional lymph node of an immunogenic composition comprising a recombinant vaccinia virus encoding IL-2 and autologous or syngeneic DCs or DC/MNs pulsed with an antigen preparation comprising enucleated cytosol and cell membranes from tumor cells infected with a recombinant vaccinia virus encoding IL-2, wherein the antigen preparation is derived from tumor cells which are the same tumor cells or the same type of tumor cells present in the mammal.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-59 and 80-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The claims recite dosages and ranges of dosages using the term "about". The term "about" is indefinite in that it is a relative term with no fixed metes and bounds. As such the metes and bounds of the claims cannot be determined based on the use of the term "about".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 rejected under 35 U.S.C. 103(a) as being unpatentable over Nestle et al. (1998) Nat. Med., Vol. 4, No. 3, 328-332 in view of Sivanandham et al. (1994) J. Immunol. Immunother., Vol. 38, 259-264. The applicant claims immunogenic compositions comprising a recombinant vaccinia virus encoding IL-2 and antigen presenting cells pulsed with an antigen preparation comprising enucleated cytosol and cell membranes from tumor cells infected with a recombinant vaccinia virus encoding IL-2. The applicant further claims methods of generating an anti-tumor immune response and methods of inhibiting tumor growth in a mammal comprising the administration of said immunogenic compositions. The applicant also claims said methods and compositions wherein the antigen presenting cells are dendritic cells, wherein the composition is administered at or near lymph nodes, where the tumor cells are melanoma or colon cancer, and wherein the dosages include "about" 10X7 pfu of VV-IL-2 and "about" 10X6 antigen presenting cells. Please note that the term "about" is relative and as such can be considered to include any dosage reasonably close to the indicated limits.

Nestle et al. teaches methods of vaccinating human patients with patient-derived dendritic cells pulsed with melanoma tumor lysate, wherein 10X6 tumor lysate pulsed dendritic cells are injected into inguinal lymph nodes, and wherein the dendritic cells express at least 2 HLA class I A antigens (Nestle et al., page 328, and page 329, Table 1). Nestle et al. differs from the instant invention by not teaching that the dendritic cells are pulsed with tumor lysate from tumors infected with VV-IL2, and that the pulsed dendritic cells are administered with separate VV-IL-2.

Sivanandham et al. supplements Nestle et al. by teaching that vaccinia oncolysate prepared from VV-IL-2 infected colon tumor cells is superior to oncolysate alone in generating anti-tumor immune responses (Sivanandham et al., page 262, Figures 3 and 4). Thus, based on the motivation provided by the teachings of Sivanandham et al., that oncolysate prepared from tumor cells infected with VV-IL-2 is more immunogenic, it would have been *prima facie* obvious to the skilled artisan to substitute vaccinia oncolysate prepared from VV-IL-2 infected tumor cells for the uninfected tumor lysate taught by Nestle et al. in Nestle's methods of treating tumors by administering DCs pulsed with tumor lysate. Based on the increased efficacy of the lysate taught by Sivanandham et al. in inducing immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor immune responses *in vivo* by administering dendritic cells pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells.

Sivanandham et al. further supplements Nestle et al. by teaching that the co-administration of viral oncolysate and exogenous IL-2 improves immune responses compared to the administration of viral oncolysate alone (Sivanandham et al., page 262, Figure 3). While Sivanandham et al. teaches the administration of recombinant IL-2 with viral oncolysate, the skilled artisan would have been motivated to use the VV-IL-2 also taught by Sivanandham instead of the recombinant IL-2 to limit systemic IL-2 toxicity and to prolong the exposure of the mammal to IL-2, since Sivanandham teaches that recombinant IL-2 has a short half-life and causes toxicity in humans (Sivanandham et al., page 260, column 1). The skilled artisan would have had a

reasonable expectation of success in using directly injected VV-IL-2 to stimulate immune responses based on the data presented by Sivanandham et al. that direct injection of 2X10X6 pfu of VV-IL-2 decreases tumor burden compared to controls (Sivanandham et al., page 262, Figure 3). Thus, it would have been *prima facie* obvious to the skilled artisan at the time of filing to supplement the administration of DCs pulsed with vaccinia oncolysate with the direct administration of VV-IL-2 in order to increase anti-tumor immune responses. Based on the teachings of Sivanandham et al. that IL-2 improves immune responses to oncolysate, and that VV-IL-2 induces anti-tumor immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor immune responses by combining the administration of DCs pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells with the administration of VV-IL-2.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The

technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER